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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/080,713	COLMAN ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62,63,65,66,70-73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 62,63,65,66,70-73,75-79,82,87-90,99,100,102-110,113,118-125,131 and 133.

DETAILED ACTION

Applicants' Appeal Brief, filed 8/15/07, is partially persuasive and necessitates new grounds of rejection. Prosecution is re-opened. Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are pending and under current examination.

This action is non-final.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-73 and 102-105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

In the instant case, the recitation of placing a promoter adjacent to an endogenous gene in the nuclear genome, lacks support from the as-filed disclosure. Although the disclosure teaches placing an exogenous gene driven by an endogenous promoter, claims 70-73 and 102-105 are not drawn to this embodiment. In particular, the claims are directed to insertion of an exogenous promoter adjacent to an endogenous gene to drive expression of the endogenous gene. This fails to find support in the as-filed disclosure.

If Applicants feel that support for the claims is found in the as-filed disclosure, Applicants are invited to point specifically, by page and line number, to where this support may be found.

To the extent that the claimed methods are not described in the instant disclosure, claims 70-73 and 102-105 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. (Emphasis added).

Enablement

Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

Methods for producing a non-human transgenic mammal, comprising:

(a) *in vitro* targeted modification of an endogenous gene in the nuclear genome of a fibroblast to produce a genetically modified fibroblast;
(b) transferring the genetically modified fibroblast, or the nucleus thereof, to an enucleated oocyte to produce a viable nuclear transfer unit;
(c) activating the viable nuclear transfer unit;
(d) culturing the viable nuclear transfer unit to produce an embryo;
(e) transferring the embryo to a surrogate mother of the same species; and
(f) allowing embryo to develop to term, thereby producing a non-human transgenic mammal.

The specification does not reasonably provide enablement for

1) The breadth of modifying the nuclear genome of any somatic cell, other than fibroblast;
2) The breadth of any genetic modification, such as specific insertion of a promoter adjacent to any endogenous gene (claims 70-73, 102-105);
3) Utilizing oocytes that are not enucleated;
4) Utilizing surrogate mothers, other than that of the same species.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' arguments have been found partially persuasive. The Examiner has provided an enabled scope of enablement above. However, the breadth of the claims is not fully enabled. The Examiner addresses each argument presented in the Appeal Brief, as it pertains to the new rejection, in the body of this rejection.

Fibroblasts as use for Donor Cells/Nucleus. Even in art at the time of filing and post-filing art, the only somatic cell type that could be predictably genetically modified in culture to form an animal was a fibroblast (Schnieke et al. 1997, Science, 278:2130-2133, Applicants' IDS Document AS26, filed 4/21/04). Thomson *et al.* (**Reprod. Supp.**, 61:495-508, 2003, of record) review the state of the art of gene targeting in somatic cells for use in nuclear transfer methodologies and state that procedures to enhance the lifespan of targeted somatic cells *in vitro* are needed. In particular, Thomson states that premature senescence often occurs, which makes it difficult to confirm a targeting event in somatic cells and that cloning efficiency has been negatively correlated with passage number. See p. 501. The inefficiency and unpredictability of homologous recombination in somatic cells is supported by Polejaeva and Campbell (**Theriogenology**, 53:117-126, 2000, of record) who teach that gene targeting in somatic cells is unpredictable because of the lower frequency of homologous recombination than ES cells, and a finite capacity for number of cell divisions. Polejaeva and Campbell further discuss specific criteria for more efficient somatic cell gene targeting, such as the ability of the cells to have a high single cell-cell cloning efficiency because during drug selection, the cells must be able to expand into clonal cultures. However, they note that human dermal fibroblasts are not able to proliferate under regular culture conditions, and thus, optimization of culture conditions must be attained for success in somatic cell gene targeting. See p. 120-121. Denning (**Cloning and Stem Cells**, 3:221-231, 2001) taught that primary cells have limited proliferation capacity and any genetic modifications and nuclear transfer must be accomplished prior to senescence specifically refer to page 222, col. 1, lines 5-8]. In a study of sheep and goat primary somatic cells, Denning found that

of primary somatic cells, fibroblasts were the only cells that either grew at all from the primary cell source or has sufficient population doublings for the selection required in targeted gene transfer. Sheep primary cell cultures primarily were composed of fibroblasts after the third passage or about 12 doublings (page 224, col. 2, lines 11-13). In a similar analysis of pig primary cultures, fibroblasts, as in the sheep study, became the predominant cell-type after three passages, but, unlike sheep, pig fibroblasts underwent a crisis after 40 population doublings and had an unstable karyotype (Denning, page 224, col. 2, parag. 4 line 4 to page 225, col. 1, line 8). Additional studies of cell cultures prepared from fetal pig organs (gut, kidney, lung and mesonephros) showed that these cells senesced or entered crisis after even fewer doublings than the fibroblast cultures (page 225, col. 1-2, bridg. sent.). The art further taught at the time of filing, that the even if sufficient population doublings could be achieved for selection, many of the pure sheep targeted clones senesced before they could be expanded for nuclear transfer, meaning that targeting frequency was lower than expected (page 228, col. 1-2, bridg. sent.). Similar experiments in pigs demonstrated that all the clones senesced, and no targeted cells for nuclear transfer were obtained. Clearly, the art supports the unpredictable and underdeveloped nature of gene targeting using any somatic cell type for use in nuclear transfer methodologies, and more specifically, that candidate somatic cells that would be used for gene targeting must be able to survive multiple rounds of cell division, selection and overcome senescence. The specification fails to provide teachings or guidance for utilizing any somatic cell for gene targeting which would be further used in nuclear transfer methods. While the state of the art supports that particular cell types, such as fetal fibroblasts, can be used in the claimed methods, specific guidance must be provided to enable the breadth of the claims.

Guidance from the Specification. The specification teaches various working and prophetic examples to support the breadth of the claims. However, upon

careful review of the specification, as well as the guidance provided by the state of the art, as well as post-filing art, it has been determined that the enabled scope of the claimed invention is limited to fibroblast cells which can be specifically targeted in order to be used in nuclear transfer methods. In particular, Applicants have argued previously and in the Appeal brief that the specification provides two separate examples of targeting endogenous loci in somatic cells. Example 1 is directed to targeting of the sheep COLIA-1 locus in primary fetal fibroblast cells (see also, Appeal Brief, page 5). Example 2 discusses using fibroblast cell clones produced in Example 1. Example 3 describes placement of the COLIA-1 locus in a primary ovine fetal fibroblast cell. Example 4 is similarly directed to the fibroblast cells of Example 3. Example 6 is directed to the knockout of the alpha 1-3 galactosyltransferase in primary porcine fetal fibroblasts. Example 7 is directed to the knockout of the bovine beta-lactoglobulin gene in bovine fetal fibroblasts.

Example 5 is directed to targeting of a gene locus in primary ovine mammary epithelial (POME) cells using a promoter trap vector, BLAT3. It is known in the art that promoter trap vectors are used to enrich the probability of obtaining a positive clone. However, the mechanism of action of promoter trap vectors are random, and only work on actively expressing genes. See, for example, Marques *et al.* (J. of Biotech., 125: 185-193, 2006), and Denning (cited above), p. 226-227, bridging ¶. Applicants have only shown a single result using a specific cell line, in which Denning clearly shows that using different species (pig and sheep), or even different cell lines from the same species, results in a large variation in targeting efficiency (see pp. 227-228 and Table 2). Thus, it is maintained that although the state of the art supports the gene targeting using fibroblasts is enabled, using any somatic cell, to specifically target any gene, as recited in the claims, is not found to be enabling.

The Examiner reiterates that the enabled scope of the claimed invention is limited to fibroblasts, based upon the state of the art, as well as the working examples in the specification. It is further noted that Denning (cited above) states

that:

"Although gene targeting in mouse ES cells is now considered routine, targeting in somatic cells is a much more problematic exercise. There is little information on the frequency of homologous recombination in primary somatic cells and this is mainly restricted to human cells. In addition, the lifespan of primary cells in culture is a critical issue; unlike ES cells and transformed cell lines, primary somatic cells have a limited proliferative capacity. Genetic modification and subsequent preparation for NT must be accomplished before the cells senesce or enter crisis and transform." See pages 221-222, bridging ¶.

Denning provide detailed discussion regarding the unpredictable issues that must be addressed in development of gene targeting for NT. In particular, these factors include: 1) the efficiency of targeting of endogenous genes; 2) large variations in frequencies in targeting different loci; 3) the limited proliferative capacity of primary somatic cells. See page 229, 1st col., 2nd ¶. They further state, "Despite our capabilities in targeting the two sheep genes by homologous recombination in primary cells, we experienced significant problems in isolating populations that could be used for NT. One reason for this was the high incidence of colonies that contained mixed populations of targeted and nontargeted cells." See p. 229, 2nd col., 3rd ¶. Thus, given that the state of the art shows unpredictability with regard to specific targeting of any gene, and further, using any somatic cell, Applicants' invention has been limited to fibroblast cells, which have been shown to be capable of specific genetic modification in an endogenous gene.

Applicants' argue that they have shown that somatic cells are "equally suited" for gene targeting, when compared to commonly ES cells (see page 8 of the Appeal Brief). Additionally, Applicants argue that they do not dispute that prior to the present invention, the state of the art supported that homologous recombination in somatic cells had low frequency, but that their data contradicts any belief that somatic cells are not equally useful for homologous recombination. See page 8 of the Appeal Brief. Applicants argue that at least nine independent groups, since the publication of the instant application, have successfully targeted five different

genes, in three different species, using fifteen different targeting constructs. Thus, Applicants argue that the claimed invention is clearly enabled (see pages 9-10 of the Appeal Brief). Applicants argue that the present information differs from that known in the art, not with regard to the individual techniques used, but rather, in the success achieved by their combination. Applicants argue that they achieved success and addressed a long-felt need by combining art-known methods that were, at the time of filing, not thought to be amenable for successful combination. Applicants further argue that the Examiner has not provided any evidence to support lack of enablement of the invention as a whole, per se, but has rather based the enablement rejections on references that teach either the unpredictability of NT or homologous recombination. Applicants argue that homologous recombination is enabled, and does not require undue experimentation. In particular, Applicants argue that gene targeting technology is the same of all cells, regardless of cell type. See pages 12-13 of the Appeal Brief. Applicants argue that although the art prior to the claimed invention showed that frequencies of homologous recombination are low, they argue that gene targeting technology is the same for cells, regardless of cell type. Applicants further cite the working examples in the specification for support to show the successful gene targeting of 4 loci in four different somatic cell types. See pages 13-14 and pages 21-22 of the Appeal brief.

These arguments have been considered, but are not fully persuasive. In particular, the Examiner has determined that, based upon Applicants' working examples, specification, and the state of the art, only fibroblast cells are enabled, in the context of the claimed invention. Particularly, Applicants' working examples only use fibroblasts, except Example 5, which uses a promoter trap vector. In general, promoter trap vectors work by random integration. Even in Denning (cited above) who use a promoterless *neo* construct, which is generally thought to be the most efficient form of targeting vector, they found only moderate frequencies of homologous recombination, which is consistent with that normally reported in

human somatic cells, but towards the lower end of the range reported for mouse ES cells. Additionally, even upon targeting the specific genes, Denning report significant problems in isolating populations of cells to be used for NT. See p. 229, 2nd column. It is further noted that a promoterless construct, such as that utilized by Denning and potentially by Applicants' invention, is only useful in the context of expressed genes (see Marques). Thus, given that Applicants' invention is directed to targeting any gene in any somatic cell from any species, the breadth of the claims is not enabled. It is noted that Denning is art that is filed after Applicants' effective filing date, and thus, considered post-filing art. Additionally, Applicants have not provided any guidance, teachings or evidence to overcome the unpredictibilities in the art, which have been presented in this, as well as prior Office actions.

With regard to the post-filing reports of successful gene targeting in somatic cells, and production of liveborn animals from using these somatic cells in NT methods, the Examiner responds that Applicants have not provided a specific list with these successes, such that the Examiner can evaluate them in side-by-side comparison. However, if Applicants feel that a breadth greater that "fibroblast" for the type of somatic cell used in NT methods is warranted, they are invited to provide the post-filing art, with specific citation as to the type of somatic cell used, the specific targeting vector, and any other specific information that may overcome the rejection.

The Examiner notes that on pages 21-22 of the Appeal Brief, Applicants have provided the targeting of five different genes in three different species using twelve different targeting constructs. The Examiner responds to each as follows: Lai (2002) uses fetal porcine fibroblasts (p. 1092, References and Notes, #17, 19). Kolber-Simonds (2004) uses cultured ear fibroblasts (p. 7335, 2nd column, Methods). Dai (2002) utilizes porcine fetal fibroblasts (p. 251, 2nd col., Results and Discussion). Sendai (2003) utilizes a bovine fetal fibroblast line (p. 900, 2nd col., Cells and Gene Transfection).

Takahagi (2005), Denning (2002), Wells (2002), Sendai (2006), Kuroiwa (2004), and Richt (2007) do not appear to be of record, so the Examiner has not considered these references. Additionally, Applicants arguments, on pages 22-23, do not specifically provide the somatic donor cells which were used in order to produce the liveborn animals. As above, if Applicants feel that a breadth of somatic cells, other than fibroblast is warranted, Applicants are invited to specifically provide guidance for other cell types, and any other information or evidence pertinent to this rejection.

Applicants argue that while the Examiner has characterized NT inefficiency as unpredictability, Applicants argue that the two concepts are distinguishable, and that one skilled in the art would not know if any given attempt would work, but one skilled in the art would know that within a set number of attempts, a certain percentage would work, and that percentage is acceptable within the art, and such experimentation would not be considered "undue".

These arguments are found to be persuasive in the context of gene targeting using fibroblast cells because the cited art (above and of record), as well as the guidance from the specification, and working examples, provide enablement only for gene targeting in fibroblast cells.

Applicants argue that claim 131 is fully enabled. In particular, they cite McCreath (2000) and Suraokar and Bradley (2000) as evidence that gene targeting and somatic NT were well-established in their respective arts. See page 12 of the Appeal Brief.

In response, the Examiner notes that McCreath teaching using primary fetal fibroblasts. Similarly, Suraokar cite McCreath, and are therefore discussing utilizing fibroblasts for gene targeting. Thus, these pieces of art support the Examiner's position with regard to the enabled scope of the claimed invention.

Nuclear Transfer. Apps argue that they are not interested in studying the mechanisms underlying the cloning process, but rather, are using technology that

has existed for the past ten years. Apps argue that through their own business model, they clearly demonstrate that NT is a routine technology that can be used successfully as a basis for productive biotechnology business. In particular, Applicants argue that they have provided Declarations from those skilled in the art whom both state that this invention is typical of the amount of experimentation in the NT art. See page 15-16 of the Appeal Brief, and the Piedrahita and Ayares Declarations. Applicants argue that the Examiner has not provided any evidence to contradict the high level of experimentation acceptable in the cloning art, rather, the Examiner has provided references that describe variables which may affect the overall efficiency of the process, or describe reasons why the process is inefficient. Applicants argue that any somatic cell donor may be used in NT technology, and that to date at least thirty types of somatic donor cells have been used to clone at least fifteen different animals. See page 17 of the Appeal Brief.

The Examiner finds the Declarations and arguments persuasive with respect to the enabled scope of fibroblast. However, it is maintained that it would have required undue experimentation for one of skill in the art to practice the claimed invention by genetically modifying any somatic cell, other than a fibroblast, for use in NT. This is due to the unpredictable factors set forth in Denning, Thomson and Marques (cited above), with regard to specifically targeting any somatic cell, other than a fibroblast cell.

The Examiner further responds to Applicants' arguments (page 18 of the Appeal Brief) with regard to utilizing somatic cells in NT methods to produce live born animals, that the rejection of record and as presented in the instant Office action, is directed to the specific targeting of a somatic cell, and then utilizing this somatic cell in methods of nuclear transfer. The Examiner contends that it would have required undue experimentation, in view of the unpredictability in the art, to utilize any other somatic cell, other than a fibroblast, to specifically target a gene sequence, and then use the resultant cell to produce a transgenic animal by NT.

The Examiner further responds to Applicants' statement (p. 18, 2nd ¶) that the Piedrahita Declaration is not directed to the subject matter at hand. This Declaration is directed to using non-transfected somatic cells (*i.e.*, the claimed invention is directed to using transfected somatic cells). Thus, the Examiner was not intending to suggest that Applicants provide evidence to show their invention was routine. The Examiner's response is directed to the fact that the Declaration provided is not within the scope of the claimed invention, particular with regard to the requirement of the claimed invention to specifically modify the nuclear genome of a somatic cell. The Piedrahita Declaration does not address this point.

Recipient Cells. Applicants have argued that there are three types of oocytes that can be used in NT, and thus, one of skill in the art would know how to select the appropriate oocyte, two cell embryo or zygote as a recipient cell to produce a viable NT unit (see pages 18-19 of the Appeal Brief).

These arguments are not persuasive. In particular, the claims do not recite that the oocyte is enucleated. Thus, the claims encompass utilizing an diploid oocyte/two-cell embryo or zygote that would produce a tetraploid embryo. Although Applicants have stated that this oocyte/two-cell embryo or zygote is "capable of" producing a viable embryo, there is no enabled scope for oocytes/two-cell embryo or zygotes, other than those that are enucleated, in the context of the claimed invention. It should be made clear that, the enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. "Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." *Vaeck*, 947 F.2d at 495, 20 USPQ2d at 1444; *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404; *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought

in a claim bear a reasonable correlation to the scope of enablement provided by the specification)." *In re Wright* (CAFC) 27 USPQ2d 1510 at 1513.

The Examiner has provided the enabled scope, with regard to the claimed invention, and has incorporated NT methods in this scope. Thus, the Examiner does not address Applicants' arguments regarding Campbell, Li, McEvoy (pages 19-21 of the Appeal Brief) because these are no longer relevant to the enabled scope.

Species/Genus. Applicants argue that whether or not a surrogate mother can carry an embryo to term is an inherent limitation known to those of skill in the art. Applicants argue that one of skill in the art would be able to determine a suitable host as a surrogate mother. The Examiner maintains that the specification does not provide specific guidance for a suitable host surrogate mother, for the breadth claimed. Although the specification teaches that a sheep can be a suitable recipient for bovine, ovine and porcine (p. 19, lines 1-9), the claims are broadly directed to production of any non-human mammal. The specification fails to provide specific guidance, for the breadth of the claims, with regard to a suitable recipient mother. Accordingly, it is reiterated that Applicants amend the claims to clarify that the NT unit, embryo and surrogate mother are of the same species, in order to enable the claim.

Genotype/Phenotype. Applicants argue that they are perplexed by this rejection, as the claims are directed to methods of producing genetically modified animals. Thus, a person of skill in the art would be producing the transgenic animals, and would obviously be able to predict the resultant phenotype/genotype, because they designed the transgenic animals. Applicants argue that the claims do not include limitations about the levels of the transgenic product, the consequence of the product, and the resulting phenotype of the animal. Applicants argue that one of skill in the art could make and used the invention. See page 24 of the Appeal Brief.

These arguments are not persuasive. Certain of the claims are directed to targeting using a specific promoter, (see claims 70-73, 102-105, for example) or specific gene inactivation or modifications (see, for example, claims 123-125). It is reiterated that although one of skill in the art may be able to identify a transgenic animal, one could not predict what phenotype this animal would exhibit. The art of record clearly supports that the resultant phenotype in a transgenic animal is unpredictable. The claims do not provide a specific phenotype. Thus, without a particular phenotype, there is no enabled use of the particular animal. Applicants have not provided specific guidance with regard to the embodiments that encompass these specific genetic modifications, and one of skill would not be able to rely upon the art to predict the phenotype of the resultant animal. The instant claims are not enabling because they claim transgenic animals which do not have an apparent phenotype, and thus, one of skill would not know how to use these animals. The state of the art is such that one could not predict the phenotype of any transgenic animal (as broadly encompassed in the claimed methods). The skilled artisan could not predict this phenotype, based upon the state of the art. If the phenotype is unknown and unpredictable, then one of skill in the art could not use these animals for any of the contemplated uses.

Accordingly, for the reasons cited above, it would have required undue experimentation for the skilled artisan to carry out the claimed methods, with a predictable degree of success, to implement the invention as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 62, 63, 65, 66, 70-73, 75-79, 82, 87-90, 99, 100, 102-110, 113, 118-125, 131, 133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 62 is unclear. Step (a) of the claim recites modifying the nuclear genome of a somatic cell with a normal karyotype at an endogenous locus. The metes and bounds of this phrase cannot be determined. In particular, as written, the nuclear genome is modified using a normal karyotype. A normal karyotype cannot modify a genome, or an endogenous locus. Appropriate correction is required. Claims 63, 65-66, 70-73, 75-79, 82, 87-89 depend from claim 62. Claim 90 is similarly unclear as it recites the same language. Claims 99, 100, 102-110, 113, 118-125 depend from claim 90. Claim 131, 133 are similarly unclear.

Claims 70 and 102 are unclear. The claims recite placing a promoter adjacent to an endogenous gene. It is unclear what the metes and bounds of the term "adjacent" encompass. The term "adjacent" merely encompasses next to the gene. This could be upstream or down stream of the gene. Furthermore, there is no language to show that the promoter is operably linked to the gene, such that expression would occur. Claims 71-73 depend from claim 70; claims 103-105 depend claim 102. Appropriate correction is required.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Campbell *et al.* (WO 97/07669, published 6 March 1997, Applicants' IDS).

Campbell teach methods of producing transgenic animals via nuclear transfer (see Abstract). They teach methods of nuclear transfer, to introduce quiescent cells arrested at G0 into enucleated oocytes (p. 9, lines 1-3 and lines 29-31) and the fusion and activation of the resultant NT unit (page 13), the activation of the resultant cell (p. 14), and then the transferring of the embryo to a surrogate mother in order to develop the embryo to term (p. 15, lines 11-19; p. 18, lines 21-33; p. 20, lines 1-23). They teach that transgenic animals that can be produced by their methods pertain to animals wherein an endogenous gene has been, "deleted, duplicated, activated or modified ..." (p. 6, lines 29-34). They additionally suggest that these modified cell populations include gene additions, gene knockouts, gene knock ins and other gene modifications, and optionally the cells may be transfected

with suitable constructs and with or without selectable markers (p. 20, lines 10-12). They teach that their methods can be used in to produce any animal (p. 5, lines 10+). They teach that the animal can be bred (p. 17, lines 15-19). They teach that the donor nucleus may contain one or more transgenes, and that this genetic modification may be introduced by methods such as electroporation, or lipofectin (p. 7, lines 1-11). They teach that the donor cell can be any somatic cell of normal karyotype, including fibroblasts (p. 7, lines 13+). They teach that the cells are quiescent and in G0 state (p. 8, lines 13-22). They teach serum starvation to produce the G0 cells (p. 8, lines 25-29).

Thus, Campbell provide sufficient motivation for the claimed invention, in that they teach genetic modification of a somatic cell with normal karyotype, they teach utilizing this somatic cell in methods of nuclear transfer in order to produce liveborn animals (claims 62, 90, 131, 133). They teach producing cattle, sheep, goats, horses, pigs, and rodents (claim 63). They teach that the genetic targeting even can result in activation, modification, addition, or knockout (claims 65-66, 99-100). They teach using constructs with a selectable marker (claims 75,106). They teach the genetic targeting event is mediated by lipofection (claims 82, 113, 122) or by electroporation (claim 121). They teach utilizing epithelial cells or fibroblasts (claims 87, 118). They teach that the cells are quiescent and in G0 state (claims 88, 119), and teach producing these G0 cells by serum starvation (claims 89, 120).

Accordingly, given the teachings of Campbell, it would have been obvious for one of skill in the art to produce a transgenic animal, as that instantly claimed, with a reasonable expectation of success. One of ordinary skill would have been sufficiently motivated to produce transgenic animals by nuclear transfer, as suggested by Campbell, to reduce the number of recipients, to increase numbers of founders using clonal donor cells, to allow subtle genetic alteration by gene targeting, for the production of transgenic, not chimeric animals, and finally, for the

selection of specific cells which have genetic modification(s) of interest, prior to the generation of the whole animal. See page 6, lines 1-20.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 76-79, 107-110, 123-124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell as applied to claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 above, and further in view of d'Apice *et al.* (U.S. Pat. No. 5,849,991 published December 15, 1998).

Campbell teach methods of producing transgenic animals via nuclear transfer (see Abstract). They teach methods of nuclear transfer, to introduce quiescent cells arrested at G0 into enucleated oocytes (p. 9, lines 1-3 and lines 29-31) and the fusion and activation of the resultant NT unit (page 13), the activation of the resultant cell (p. 14), and then the transferring of the embryo to a surrogate mother in order to develop the embryo to term (p. 15, lines 11-19; p. 18, lines 21-33; p. 20, lines 1-23). They teach that transgenic animals that can be produced by their methods pertain to animals wherein an endogenous gene has been, "deleted, duplicated, activated or modified ..." (p. 6, lines 29-34). They additionally suggest that these modified cell populations include gene additions, gene knockouts, gene knock ins and other gene modifications, and optionally the cells may be transfected with suitable constructs and with or without selectable markers (p. 20, lines 10-12). They teach that their methods can be used in to produce any animal (p. 5, lines 10+). They teach that the animal can be bred (p. 17, lines 15-19). They teach that the donor nucleus may contain one or more transgenes, and that this genetic modification may be introduced by methods such as electroporation, or lipofectin (p. 7, lines 1-11). They teach that the donor cell can be any somatic cell of normal karyotype, including fibroblasts (p. 7, lines 13+). They teach that the cells are

quiescent and in G0 state (p. 8, lines 13-22). They teach serum starvation to produce the G0 cells (p. 8, lines 25-29).

Although Campbell do not specifically teach knockout of the alpha 1-3 galactosyltransferase gene, prior to the time of the claimed invention, d'Apice teach methods for reduction or elimination of the hyperacute rejection response in human, in particular, by producing knockout animals which lack or have reduced alpha 1-3 galactosyltransferase activity (see col., 1, Field of Invention). They specifically teach the porcine sequence (Figure 4), but teach that variations of these sequences can readily be generated by the skilled artisan (col. 2-3, bridging ¶). They teach generation of mammals lacking alpha 1-3 galactosyltransferase (col. 4, lines 54-60), wherein both copies of the gene are inactivated (col. 5, lines 1-2). d'Apice further teach that their targeting construct can contain a selectable marker, including the gene imparting resistance to the antibiotic G418 (col. 13, lines 20-22). They teach any marker that is suitable for inclusion in a knockout marker can be used (col. 13, lines 26-27). They specifically teach that GFP can be used in a construct, in order to detect gene targeting events. Col. 59, lines 5-9 and lines 23-33.

Accordingly, in view of the combined teachings of Campbell and d'Apice, it would have been obvious for one of skill in the art to modify the teachings of Campbell, to specifically inactivate the alpha 1-3 galactosyltransferase gene in a somatic cell, and to use this somatic cell in methods of nuclear transfer in order to produce an animal, wherein the alpha 1-3 galactosyltransferase gene has been inactivated, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make this modification, given Campbell's teachings for increasing efficiency of producing transgenic animals, and further, given d'Apice's teachings for the need in the art to produce animals whose organs can then be used for xenotransplantation, wherein the knockout of the alpha 1-3 galactosyltransferase gene reduces or eliminates the hyperacute rejection response. Additionally, one of skill in the art would have been motivated to modify

the targeting construct used to target a somatic cell, with any of the markers or promoters suggested by d'Apice, and instantly claimed, because these techniques were well within the skill of the ordinary artisan. One of skill in the art would readily recognize utilizing various marker genes in order to select for clones when performing transfection experiments.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 70, 73, 77, 102, 105, 107, 108, 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell as applied to claims 62, 63, 65, 66, 75, 76, 82, 87-90, 99, 100, 106, 113, 118, 119, 120-122, 131 and 133 above, and further in view of Kucherlapati *et al.* (WO 94/02602, published February 3, 1994).

Campbell is described above. Campbell does not specifically teach inactivation of an endogenous immunoglobulin gene. However, prior to the time of the claimed invention, Kuncherlapati teach the production of non-human mammals with inactivated endogenous Ig loci (see Abstract). In particular, Kuncherlapati teach an art-recognized interest in producing xenogeneic human monoclonal antibodies using transgenic animals (p. 2, lines 23-31). They teach methods of knocking out of the endogenous Ig loci and knocking in of human Ig (p. 6, lines 6-12; p. 10, lines 10-12). Kuncherlapati teach knockout of the endogenous Ig in mouse ES cells, they suggest producing any mammalian host using their methods (p. 10, lines 1-2, pages 16-17). Additionally, Kuncherlapati teach that their targeting constructs can contain various marker genes, including those which confer G418 resistance (p. 16, lines 34-36). Kuncherlapati further teach that the targeting construct may include a replication system, including a promoter (p. 18, line 8).

Accordingly, given the combined teachings of Campbell and Kuncherlapati, it would have been obvious for one of ordinary skill in the art to use the technology of Campbell, and inactivate an endogenous Ig gene in a somatic cell, with a reasonable

expectation of success. Although Kuncherlapati teach knockout of the endogenous Ig in mouse ES cells, Campbell provides the teachings and suggestion to use a somatic cell, and then use the modified somatic cell in methods of NT to produce transgenic animals. One of ordinary skill in the art would have been sufficiently motivated to knockout an endogenous Ig gene, as supported by Kuncherlapati, who teach that it is an art-recognized goal to produce xenogeneic specific binding proteins, such as human monoclonal antibodies (p. 2, lines 23-32) by production of transgenic animals. Additionally, one of skill in the art would have been motivated to modify the targeting construct used to target a somatic cell, with any of the markers or promoters suggested by Kuncherlapati, because these techniques were well within the skill of the ordinary artisan. One of skill in the art would readily recognize utilizing various marker genes in order to select for clones when performing transfection experiments.

With regard to claim 73, this claim only requires that the promoter directs expression of one gene in fibroblast cells. This does not exclude a promoter that directs expression in all cells, such as a ubiquitously expressed promoter.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Peter Paras, SPE of Art Unit 1632, at (571) 272-4517. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Thaian N. Ton/
Primary Examiner
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